Lipids in Health and Disease

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Associations of the atherogenic index of plasma with 28-day in-hospital mortality in patients with acute myocardial infarction: a retrospective cohort study from the eICU

Yan Wang[1,2] and Hong-Fei Zhang[1,2*]

Abstract

Background Despite substantial advancements in treatment strategies, acute myocardial infarction (AMI) continues to exhibit high mortality. Recent research has identified the atherogenic index of plasma (AIP) as a significant measure of cardiovascular outcomes. However, the relationship between the AIP and 28-day mortality during hospitalization in AMI patients remains to be further clarified.

Methods A retrospective analysis was conducted based on data sourced from the eICU Collaborative Research Database, encompassing records of 2,517 AMI patients treated in 208 critical care facilities across the U.S. from 2014 to 2015. AIP measurements were derived via log10 (triglyceride/high-density lipoprotein cholesterol) calculations. The primary endpoint was 28-day in-hospital mortality. The analysis utilized adjusted multivariable logistic models with restricted cubic splines for nonlinear associations. Subgroup analyses were performed to evaluate the relationships between AIP and mortality across various demographic and clinical subgroups. These subgroups included age, sex, body mass index (BMI), congestive heart failure, intubation status, mechanical ventilation, pneumonia, diabetes mellitus, antihyperlipidaemic agents, and AMI types.

Results Among the 2,517 patients enrolled in the cohort (median age: 64.42 years), 138 (5.48%) died within 28 days. The analysis revealed a nonlinear association between the AIP and mortality, presenting a J-curve shape with a threshold of 0.60 (*P* for nonlinearity = 0.028). Each 0.1-unit elevation above 0.60 corresponded to a 22% increased mortality risk (adjusted OR = 1.22, 95% CI: 1.09–1.36; *P* = 0.0004). The highest AIP quartile had a 112% greater mortality risk than the lowest quartile (adjusted OR = 2.12, 95% CI: 1.15–3.88; *P* = 0.0154). Subgroup analyses revealed consistent patterns across the strata.

Conclusion The relationship between the AIP and 28-day hospital mortality in AMI patients may be characterized by a J-shaped curve, where elevated AIP values are associated with increased mortality risk.

Keywords Acute myocardial infarction, Atherogenic index of plasma, Hospital mortality, EICU database

*Correspondence:
Hong-Fei Zhang
zhanghongfei@smu.edu.cn
[1] Department of Anesthesiology, Zhujiang Hospital, Southern Medical University, Guangzhou 510280, China
[2] Institute of Perioperative Medicine and Organ Protection, Zhujiang Hospital of Southern Medical University, Guangzhou 510280, China

Introduction

Among cardiovascular disorders, acute myocardial infarction (AMI) is a critical health emergency. According to the 2023 report from the American Heart Association, despite therapeutic advances, the prognosis of AMI patients remains suboptimal [1]. Specifically, in developing countries, 28-day hospital mortality among AMI

patients remains elevated due to multiple contributing factors, including inadequate health care resources and delayed treatment [2, 3].

The atherogenic index of plasma (AIP), which is derived from log10 (triglycerides/high-density lipoprotein cholesterol; TG/HDL-C), represents an innovative lipid metric that quantifies the ratio of atherogenic to protective lipoproteins [4, 5]. Studies have shown that the AIP not only more effectively reflects atherogenic dyslipidaemia compared to traditional lipid parameters but also plays a vital role in evaluating cardiovascular outcomes [6, 7]. Emerging evidence has demonstrated the clinical significance of elevated AIP values across multiple cardiovascular conditions, including diabetes-related complications, coronary pathology, arterial disorders, and cerebrovascular events [8, 9].

Current evidence on the link between AIP and cardiovascular outcomes presents inconsistent findings. Population-based research by Qin et al.[10] identified positive correlations with cardiovascular mortality, whereas subsequent cohort analyses revealed nonlinear patterns (specifically U- or J-shaped associations) with mortality outcomes [11, 12]. Notably, the AIP has demonstrated strong associations with cardiovascular morbidity and the degree of coronary artery disease severity, particularly in populations with diabetes and middle-aged individuals [13]. Although the AIP is acknowledged as being a significant indicator for evaluating cardiovascular risk, the correlation between the AIP and mortality may differ according to the attributes of the population and preexisting health issues. Thus, further investigation is needed to clarify these associations and develop standardised clinical guidelines.

We hypothesised that in patients with AMI, AIP values are associated with 28-day in-hospital mortality. In this retrospective multicentre cohort study using the eICU Collaborative Research Database from 208 ICUs across the United States (2014–2015), we aimed to identify the threshold at which AIP significantly increases mortality risk in AMI patients. This determination could inform risk stratification and guide metabolic management to improve clinical outcomes.

Materials and methods

Data sources and ethics

This study utilised data from the eICU-CRD, which is a multicentre database that collected the data of clinical records from 208 U.S. intensive care units from 2014–2015 [14]. The database encompasses extensive clinical measurements, including biochemical analyses and physiological monitoring data. To ensure the confidentiality of the patients, all of the personal identifiers were removed, and random codes were assigned instead of patient identifiers. Consequently, the need for individual patient consent or ethics approval was waived. Researcher Yan Wang was granted access to this database after completing the required research ethics training (Certification: 66418889).

Study population

This study analysed ICU admissions with confirmed AMI diagnoses based on ICD-9 criteria (Supplementary Material). Exclusions were applied to participants who fulfilled any of the following criteria: (1) those with subsequent ICU visits, (2) those with ICU stays of less than 24 h, (3) individuals under the age of 18, or (4) those with missing triglyceride or HDL-cholesterol measurements following ICU admission or due to systematic errors. The study cohort ultimately included 2,517 eligible patients. A flowchart detailing the study's process is depicted in Fig. 1.

Study variables

Definition of the atherogenic index of plasma

Primary exposure was quantified using the atherogenic plasma index, calculated as the logarithm of the TG/HDL-C ratio (mmol/L). Lipid analyses adhered to standardised protocols established by national health authorities and utilised peripheral blood samples obtained during the initial 24 h postadmission. The eICU database lacks data on the exact timing of these measurements relative to the initiation of lipid-lowering therapy. However, 13.43% of the patients were receiving antihyperlipidaemic agents at the time of admission, whereas 86.57% of the patients were not receiving these agents (Table 1). This variability may introduce potential bias to the study, and we have discussed its implications in the discussion section.

Assessment of variables

The initial data collection was concentrated on the period immediately after patient admission, specifically within the first 24 h. Physiological metrics, encompassing temperature, respiratory status, and hemodynamic readings, were derived from ApacheApsVar entries. Patient demographic information was gathered from both the individual records and the Apache Patient Results database. Comprehensive laboratory data, including lipid profiles, renal function indicators, and metabolic assessments, were retrieved from the corresponding laboratory logs. Additional variables, including critical care interventions (such as intubation, ventilation support, and renal replacement therapy), duration of ICU stay, and duration of hospital stay, were derived from the ApacheApsVar table. Relevant comorbidities (including pulmonary conditions, metabolic disorders, cardiac complications, and

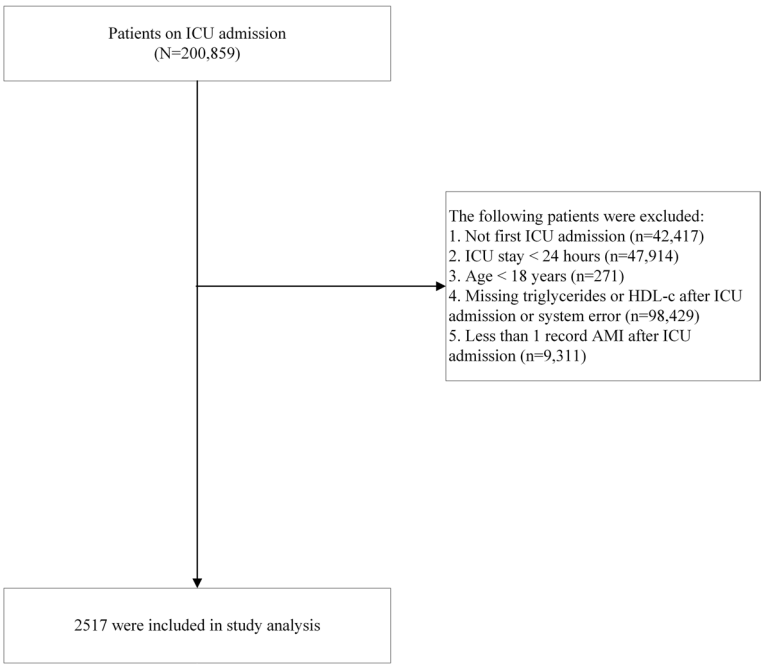

Fig. 1 Flowchart of the study population

renal diseases) and acute myocardial infarction subtypes (ST-segment elevation myocardial infarction [STEMI] and non-ST-segment elevation myocardial infarction [non-STEMI]) were identified from the diagnostic table. Treatments including antihyperlipidaemic agents, coronary revascularisation procedures (such as percutaneous coronary intervention [PCI]), and mechanical circulatory support (such as intra-aortic balloon pump [IABP]) were identified from the treatment table. Missing data were managed using multiple imputations.

Outcomes

The primary outcome assessed was all-cause hospital mortality within 28 days following ICU admission.

Statistical analysis

Statistical analyses were performed using EmpowerStats (www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) and version 4.2.1 of R software. Continuous variables were presented as mean ± standard deviation (SD) or medians with interquartile ranges (IQRs), contingent upon the assessment of data distribution normality. The frequency distributions were used to summarise the categorical variables—between-group analyses employed parametric or nonparametric methods, as appropriate.

The AIP-mortality association underwent multistage analysis. Initially, generalised additive models (GAMs) were employed to construct nonlinear models, thereby elucidating the dose–response relationship (Fig. 2). We subsequently implemented logistic models to generate crude and adjusted risk estimates with 95% confidence intervals. Covariates for adjustment were selected based on clinical relevance and if they altered the effect estimates by > 10% [15]. The final analytical framework incorporated demographics, comorbidities, clinical parameters, and vital signs.

Further analysis was conducted using a two-segment linear regression model to detect potential threshold effects of AIP levels on mortality (Table 3). The optimal inflection point was determined via iterative analysis across predetermined intervals, whereby the point maximising model likelihood was selected. Model comparison between simple linear and two-piecewise approaches utilised likelihood ratio testing. Confidence intervals for the threshold point were generated via bootstrap resampling techniques [16] by following established statistical protocols [17, 18].

The methodological stability of our findings underwent rigorous validation via multiple analytical approaches. Data completeness was addressed via iterative imputation procedures. To assess the potential impact of residual confounding factors, E-value calculations were conducted [19], which provided quantitative estimates of the confounding strength that were necessary to invalidate our primary observations. All of the statistical inferences were derived by using a bilateral significance threshold of 0.05.

Table 1 Baseline characteristics of participants

AIP quartile	Q1 (−0.56–0.26)	Q2 (0.26–0.47)	Q3 (0.47–0.70)	Q4 (0.70–1.99)	*P*-value
N	629	629	629	630	
Demographics					
Age (years)	68.26 (12.93)	66.24 (12.88)	63.42 (13.07)	59.76 (12.32)	< 0.001
Gender, *n* (%)					< 0.001
Male	262 (41.65%)	218 (34.66%)	198 (31.48%)	170 (26.98%)	
Female	367 (58.35%)	411 (65.34%)	431 (68.52%)	460 (73.02%)	
Admission weight (kg)	78.55 (20.55)	85.55 (20.70)	89.00 (24.01)	93.37 (22.42)	< 0.001
Admission height (cm)	169.22 (11.04)	171.13 (10.67)	171.58 (10.12)	172.38 (10.81)	< 0.001
BMI (kg/m^2)	27.39 (6.56)	29.22 (6.60)	30.21 (7.35)	31.32 (7.22)	< 0.001
Ethnicity, *n* (%)					< 0.001
Caucasian	469 (75.89%)	491 (79.07%)	480 (77.67%)	519 (83.84%)	
African American	89 (14.40%)	57 (9.18%)	56 (9.06%)	27 (4.36%)	
Hispanic	36 (5.83%)	40 (6.44%)	52 (8.41%)	45 (7.27%)	
Asian	15 (2.43%)	24 (3.86%)	20 (3.24%)	19 (3.07%)	
Native American	0 (0.00%)	1 (0.16%)	2 (0.32%)	3 (0.48%)	
Other/Unknown	9 (1.46%)	8 (1.29%)	8 (1.29%)	6 (0.97%)	
Unit types					0.673
Medical-Surgical ICU	249 (39.59%)	231 (36.72%)	215 (34.18%)	218 (34.60%)	
Neurological ICU	28 (4.45%)	22 (3.50%)	22 (3.50%)	26 (4.13%)	
Coronary Care Unit	164 (26.07%)	169 (26.87%)	158 (25.12%)	171 (27.14%)	
Cardiothoracic ICU	118 (18.76%)	143 (22.73%)	156 (24.80%)	151 (23.97%)	
Medical ICU	13 (2.07%)	8 (1.27%)	12 (1.91%)	8 (1.27%)	
Surgical ICU	11 (1.75%)	14 (2.23%)	11 (1.75%)	8 (1.27%)	
Cardiac Surgery ICU	11 (1.75%)	10 (1.59%)	17 (2.70%)	15 (2.38%)	
Cardiac ICU	35 (5.56%)	32 (5.09%)	38 (6.04%)	33 (5.24%)	
Comorbidities					
COPD, *n* (%)	46 (7.31%)	27 (4.29%)	22 (3.50%)	23 (3.65%)	0.005
CHF, *n* (%)	73 (11.61%)	69 (10.97%)	53 (8.43%)	46 (7.30%)	0.042
DM, *n* (%)	59 (9.38%)	83 (13.20%)	61 (9.70%)	79 (12.54%)	0.094
Pneumonia, *n* (%)	35 (5.56%)	33 (5.25%)	29 (4.61%)	28 (4.44%)	0.790
CKD, *n* (%)	9 (1.43%)	5 (0.79%)	3 (0.48%)	6 (0.95%)	0.353
ESRD, *n* (%)	12 (1.91%)	10 (1.59%)	7 (1.11%)	11 (1.75%)	0.706
AMI, *n* (%)					0.806
STEMI	299 (47.54%)	299 (47.54%)	287 (45.63%)	289 (45.87%)	
non-STEMI	313 (49.76%)	317 (50.40%)	327 (51.99%)	331 (52.54%)	
Vital signs within 24 h after ICU admission					
Temperature_min (℃)	36.42 (0.94)	36.40 (0.71)	36.42 (0.83)	36.39 (0.76)	0.866
Respiratory rate_min (bpm)	26.50 (10.00–36.00)	27.00 (11.00–35.00)	27.00 (11.00–36.00)	25.00 (10.00–35.00)	0.160
Heart rate_min (bpm)	89.45 (31.02)	88.59 (30.71)	86.74 (29.23)	88.41 (30.14)	0.466
MAP_min (mmHg)	85.22 (38.10)	87.77 (40.20)	89.93 (38.20)	88.03 (37.69)	0.205
Laboratory variables					
LDL-c (mg/dL)	87.95 (37.98)	94.97 (38.82)	101.08 (40.36)	98.49 (43.90)	< 0.001
HDL-c (mg/dL)	53.75 (13.95)	41.96 (8.85)	35.98 (7.72)	29.27 (8.22)	< 0.001
Total cholesterol (mg/dL)	153.34 (41.43)	155.01 (43.61)	163.11 (45.95)	174.34 (54.32)	< 0.001
Triglycerides (mg/dL)	64.67 (19.59)	98.30 (20.94)	137.80 (33.23)	255.51 (160.78)	< 0.001
BUN (mg/dL)	18.00 (13.00–25.00)	17.00 (13.00–24.00)	15.00 (12.00–23.00)	16.00 (12.00–23.00)	0.008
Serum creatinine (mg/dL)	0.93 (0.76–1.25)	0.95 (0.79–1.26)	0.94 (0.77–1.20)	0.94 (0.78–1.19)	0.865
Glucose(mg/dl)	123.00 (104.00–156.00)	128.00 (109.00–167.00)	126.00 (106.00–169.75)	130.00 (107.00–185.00)	0.003

Table 1 (continued)

AIP quartile	Q1 (−0.56–0.26)	Q2 (0.26–0.47)	Q3 (0.47–0.70)	Q4 (0.70–1.99)	*P*-value
Advanced life support					
Intubation, *n* (%)	48 (7.88%)	43 (7.07%)	35 (5.79%)	57 (9.42%)	0.135
Mechanical ventilation, *n* (%)	79 (12.97%)	85 (13.98%)	52 (8.60%)	78 (12.89%)	0.032
Renal replacement therapy, *n* (%)	8 (1.31%)	8 (1.32%)	5 (0.83%)	13 (2.15%)	0.274
Treatment					
Antihyperlipidaemic agents, *n* (%)	77 (12.24%)	92 (14.63%)	81 (12.88%)	88 (13.97%)	0.655
IABP, *n* (%)	14 (2.23%)	9 (1.43%)	7 (1.11%)	10 (1.59%)	0.457
PCI, *n* (%)	19 (3.02%)	24 (3.82%)	26 (4.13%)	33 (5.24%)	0.266
Outcomes					
LOS Hospital (day)	3.55 (2.41–6.18)	3.76 (2.50–6.98)	3.34 (2.25–6.15)	3.14 (2.10–6.32)	0.002
LOS ICU (day)	1.91 (1.46–3.12)	1.89 (1.40–3.08)	1.84 (1.36–2.82)	1.79 (1.27–2.94)	0.018
Hospital 28-day mortality	36 (5.72%)	35 (5.56%)	27 (4.29%)	40 (6.35%)	0.461

Categorical variables were displayed as *N* (%), and continuous variables were digested as median (interquartile range) or mean ± standard deviation

Note: Only the number of patients with positive results is shown for clarity

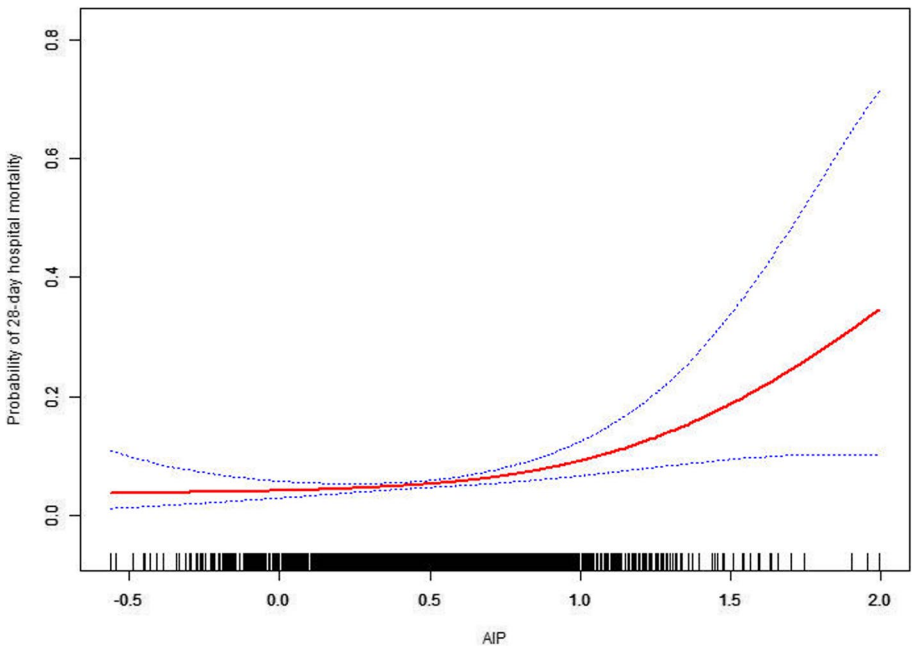

Fig. 2 Nonlinear associations between the AIP and 28-day hospital mortality adjusted for demographic characteristics, comorbidities, clinical parameters and antihyperlipidaemic agents. The red line represents the fitted curve with 95% confidence intervals (blue dotted lines); the rug plot shows the AIP distribution in the study population

Results

Baseline characteristics

The study included 2,517 patients, whose data were analyzed across AIP quartiles (Q1: −0.56–0.26; Q2: 0.26–0.47; Q3: 0.47–0.70; Q4: 0.70–1.99) (see Table 1). The mean age of patients ranged from 68.26 ± 12.93 years in Q1 to 59.76 ± 12.32 years in Q4 ($P < 0.001$). The percentage of represented females increased from 58.35% in Q1 to 73.02% in Q4 ($P < 0.001$). Table 1 compares patient demographics, clinical characteristics, and laboratory parameters across AIP quartiles. Compared with those in Q1, patients in Q4 exhibited higher BMI values (31.32 ± 7.22 vs. 27.39 ± 6.56 kg/m^2, $P < 0.001$), higher triglyceride levels (255.51 ± 160.78 vs. 64.67 ± 19.59 mg/dL, $P < 0.001$), and lower HDL-c levels (29.27 ± 8.22 vs. 53.75 ± 13.95 mg/dL, $P < 0.001$). Compared with lower quartiles, higher quartiles were associated with shorter hospital stays (3.14 vs. 3.55 days, $P = 0.002$) and lower rates

of COPD (3.65% vs. 7.31%, $P = 0.005$). The prevalence of chronic kidney disease (CKD) was low, ranging from 1.43% in Q1 to 0.95% in Q4 ($P = 0.353$). Similarly, end-stage renal disease (ESRD) prevalence remained stable across the quartiles, with Q1 at 1.91% and Q4 at 1.75% ($P = 0.706$).

For AMI, the distributions of STEMI and non-STEMI did not significantly differ across the AIP quartiles ($P = 0.806$). The prevalence of antihyperlipidaemic agents was consistently observed across the quartiles, with the Q1 prevalence observed at 12.24%, and the Q4 prevalence observed at 13.97% ($P = 0.655$). Invasive treatments such as intra-aortic balloon pump (IABP) and percutaneous coronary intervention (PCI) also demonstrated no significant variations across the AIP quartiles (IABP: Q1 at 2.23% vs. Q4 at 1.59%, $P = 0.457$; PCI: Q1 at 3.02% vs. Q4 at 5.24%, $P = 0.266$). There were no significant differences in 28-day mortality across the quartiles ($P = 0.461$). The results of the univariate logistic regression analysis are detailed in Supplementary Table S1.

Association between the AIP and 28-day hospital mortality

A nonlinear association between the AIP and mortality was observed, as illustrated in Fig. 2. Generalised additive modelling revealed complex associations between plasma atherogenic indices and acute mortality risk in patients with AMI. Statistical modelling incorporated comprehensive adjustments for physiological parameters (such as vital signs), demographic factors, comorbid conditions (including respiratory disorders, cardiac dysfunction, and metabolic diseases), intensive care metrics and antihyperlipidaemic agents.

Multivariate logistic regression analysis revealed a significant association between AIP and 28-day mortality in AMI patients after comprehensive adjustments for demographic characteristics, clinical parameters, comorbidities, and antihyperlipidaemic agents (Table 2). Variables were selected for inclusion in the models based on their clinical relevance and known associations with mortality in AMI patients. Specifically, we included variables such as age, sex, BMI, comorbid conditions, and other clinical parameters. We did not include LDL or other lipid variables (such as total cholesterol or triglycerides) in our multivariate models, to maintain the focus on the independent effect of the AIP and to avoid multicollinearity, as these lipid variables are closely related to the AIP and could complicate the interpretation of our results. Continuous variable analysis revealed that each 0.1-unit AIP increase was associated with a higher mortality probability (OR = 1.10, 95% CI: 1.03–1.17; $P = 0.0034$). Quartile analysis showed a twofold mortality risk in Q4 (≥ 0.7) compared with Q1 (OR = 2.12, 95% CI: 1.15–3.88; $P = 0.0154$). Intermediate quartiles (Q2 and Q3) did not show significant risk changes (Q2: OR = 1.33, $P = 0.3325$; Q3: OR = 1.20, $P = 0.5713$). Significant trends across AIP quartiles ($P = 0.0306$) indicate that elevated AIP independently correlates with higher mortality in AMI patients.

Threshold effect analysis showed a significant nonlinear relationship between the AIP and mortality in AMI patients within 28 days (detailed in Table 3). The overall analysis showed that each 0.1-unit rise in AIP was linked to a 10% higher mortality risk (OR = 1.10, 95% CI: 1.03–1.17; $P = 0.0034$). However, a two-piecewise linear regression model indicated a crucial threshold at AIP = 0.60. Below this threshold, no significant correlation was detected (OR = 1.00, 95% CI: 0.90–1.11; $P = 0.9605$). Conversely, a 0.1-unit rise in AIP above this threshold corresponded to a 22% higher mortality risk (OR = 1.22, 95% CI: 1.09–1.36; $P = 0.0004$). The likelihood ratio test corroborated that the nonlinear model offered a significantly superior fit compared with the linear model ($P = 0.028$), thus substantiating the presence of a threshold effect at AIP = 0.60. This suggests that an AIP value exceeding 0.60 warrants increased clinical attention and may prompt the adoption of more intensive intervention measures.

Table 2 Logistic regression for AIP (per-0.1 unit) and 28-day hospital mortality in patients with AMI

Exposure	Model 1 OR (95% CI)	*P* value	Model 2 OR (95% CI)	*P* value	Model 3 OR (95% CI)	*P* value
AIP	1.04 (0.99, 1.10)	0.1091	1.12 (1.06, 1.18)	< 0.0001	1.10 (1.03, 1.17)	0.0034
AIP quartile						
Q1 (≤ 0.26)	Reference		Reference		Reference	
Q2 (0.26 to 0.47)	0.97 (0.60, 1.57)	0.9028	1.12 (0.69, 1.83)	0.6414	1.33 (0.75, 2.34)	0.3325
Q3 (0.47 to 0.70)	0.74 (0.44, 1.23)	0.2462	1.00 (0.59, 1.69)	0.9954	1.20 (0.64, 2.23)	0.5713
Q4 (≥ 0.7)	1.12 (0.70, 1.78)	0.6412	2.01 (1.23, 3.30)	0.0057	2.12 (1.15, 3.88)	0.0154
P for trend	0.8806		0.0166		0.0306	

Model 1: no adjustment

Model 2: adjusted for gender, age, ethnicity

Model 3: adjusted for gender, age, ethnicity, BMI, COPD, CHF, pneumonia, LOS Hospital, LOS ICU, intubation, mechanical ventilation, respiratory rate_min, heart rate_min, temperature_min and anti-hyperlipidemic agents

Table 3 Threshold effect analysis of AIP (per-0.1 unit increase) and 28-day hospital mortality

Models	Per-0.1 unit increase	
	OR (95% CI)	*P* value
Model I		
One line effect	1.10 (1.03, 1.17)	0.0034
Model II		
Turning point (K)	0.60	
AIP < 0.60	1.00 (0.90, 1.11)	0.9605
AIP ≥ 0.60	1.22 (1.09, 1.36)	0.0004
P value for LRT test*	0.028	
95% CI for turning point	0.50, 0.69	

Abbreviations: *OR* Odds ratios, *CI* Confidence interval, *LRT* Logarithm likelihood ratio test

We adjusted for gender, age, ethnicity, BMI, COPD, CHF, pneumonia, LOS Hospital, LOS ICU, intubation, mechanical ventilation, respiratory rate_min, heart rate_min, and temperature_min, anti-hyperlipidemic agents. *$P < 0.05$ indicates that Model II is significantly different from Model I

Subgroup analysis

Stratified analyses revealed consistent associations across most of the subgroups, with notably pronounced effects being observed in specific populations (Fig. 3). The risk factor demonstrated stronger associations with 28-day hospital mortality in males (OR = 1.13, 95% CI: 1.03–1.24), particularly in patients aged ≤ 65 years (OR = 1.33, 95% CI: 1.14–1.55). A significant age-dependent effect modification was observed (*P* for interaction = 0.0354), thereby suggesting differential risk patterns across age strata.

The association remained robust in patients with BMI > 28 (OR = 1.09, 95% CI: 1.00–1.19), those requiring mechanical ventilation (OR = 1.13, 95% CI: 1.03–1.25), and those undergoing intubation (OR = 1.10, 95% CI: 0.98–1.24). Similarly, elevated risks were observed in subjects without CHF (OR = 1.09, 95% CI: 1.01–1.17), those with pneumonia (OR = 1.17, 95% CI: 0.98–1.40), and nondiabetic patients (OR = 1.11, 95% CI: 1.03–1.18). Notably, patients not receiving antihyperlipidaemic agents had an OR of 1.11 (95% CI: 1.04–1.19) for 28-day mortality, indicating a significant risk increase. In contrast, patients receiving these agents had an OR of 1.22 (95% CI: 0.91–1.63), which did not reach statistical significance as the confidence interval included the null value of 1. The lack of significance observed may be due to the small sample size of patients undergoing lipid-lowering therapy.

In terms of AMI type, the AIP-mortality association was stronger in STEMI patients (OR = 1.18, 95% CI: 1.06–1.30) than in non-STEMI patients (OR = 1.05, 95% CI: 0.96–1.15). This finding indicates that the AIP may exert a more pronounced effect on mortality in STEMI patients. The consistency of these associations across various clinical characteristics (all other interaction *P*-values > 0.05) underscores the generalizability of our findings across diverse patient populations.

Sensitivity analysis

To assess the stability of AIP-mortality associations, multiple imputation methods were employed to address missing covariate data. The analyses that were conducted on the imputed datasets produced outcomes that aligned with our primary findings (see Supplementary Table S2). Furthermore, E values were computed to evaluate the potential impact of unmeasured confounders. The findings indicated robust correlations, which could only be negated by an unmeasured confounder demonstrating an odds ratio exceeding 1.74, thereby implying a high degree of resilience against potential unmeasured confounding factors.

Discussion

This retrospective cohort analysis revealed that elevated AIP is linked to higher 28-day mortality risk among AMI patients in the eICU-CRD database, which includes data from 208 U.S. ICUs (2014–2015). A key finding was the J-shaped relationship between AIP and mortality risk, with the highest risk in individuals with markedly elevated indices. Furthermore, subgroup analyses demonstrated consistent trends across the various strata. Although previous studies have examined the AIP in various cardiovascular conditions, our study offers several unique contributions: (1) an exclusive focus on AMI patients in critical care settings, thus providing population-specific insights; (2) an investigation of short-term (28-day) mortality, thereby offering immediate clinical value; (3) an identification of a precise clinical threshold via advanced statistical modelling; and (4) corroboration using multicentre data from 208 ICUs, thus ensuring broader generalisability. These features distinguish our findings from those in the literature and provide practical guidance for clinical risk stratification in AMI patients.

The findings align with several previous investigations of AIP and mortality, particularly the observed J-shaped association. Notably, a recent meta-analysis by Wu et al. showed that higher AIP values are linked to increased cardiovascular risk, supporting the critical threshold effect at AIP = 0.6 for risk stratification in AMI patients [20]. This threshold is clinically actionable, as it allows for the implementation of targeted interventions in high-risk populations. Moreover, the J-shaped association observed in our study corroborates findings from large-scale cohort studies, including those by Liu and Wang et al., which identified similar nonlinear relationships between the AIP and cardiovascular mortality [21, 22].

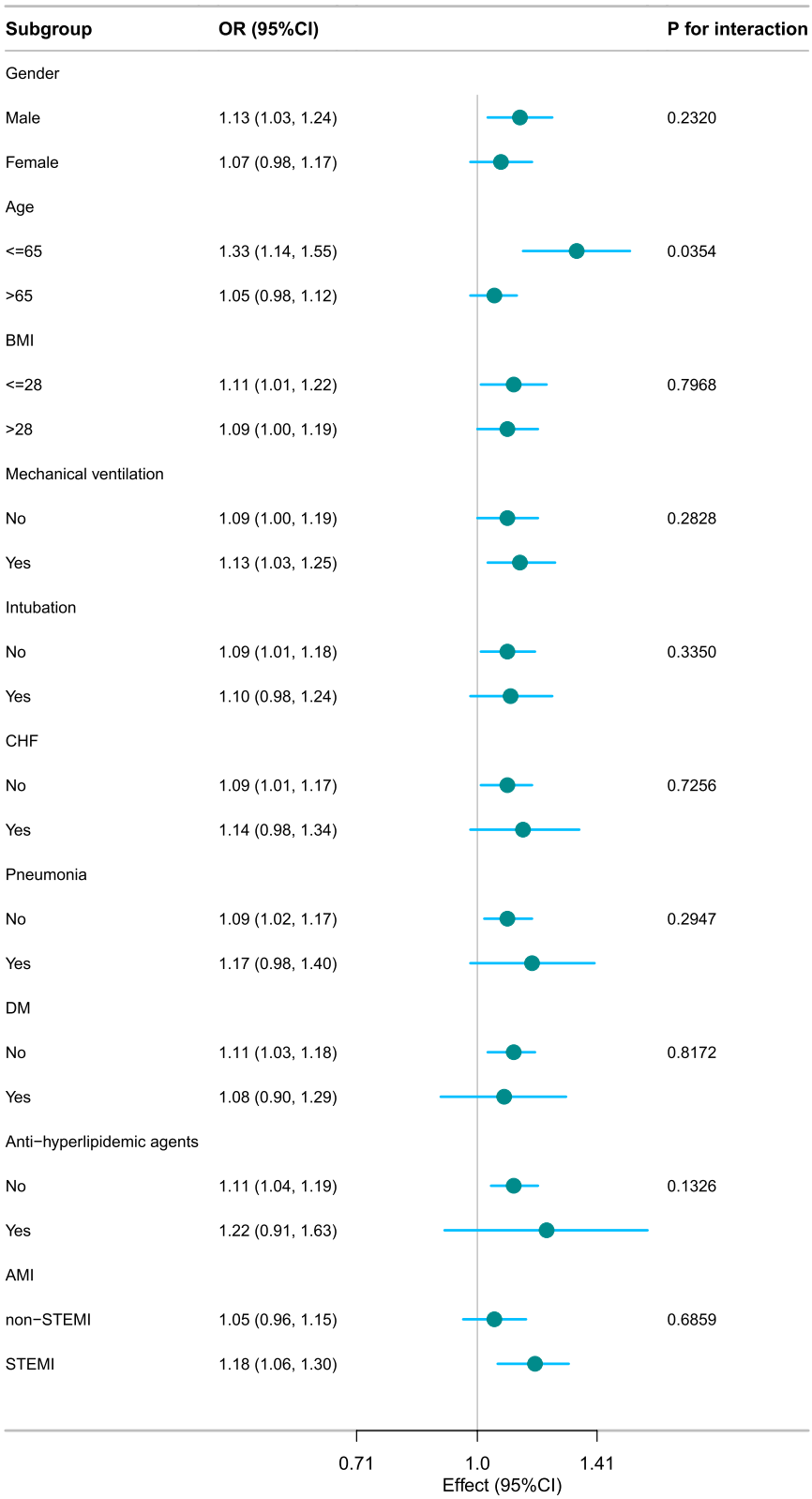

Fig. 3 Subgroup analyses of the association between the AIP and 28-day hospital mortality in AMI patients. Adjusted for all covariates except for this subgroup of variables

These studies emphasise that an elevated AIP reflects an atherogenic lipid profile, defined by increased small, dense LDL particles and reduced HDL-C levels, which may exacerbate myocardial injury via enhanced oxidative stress and impaired cholesterol efflux capacity [22, 23]. However, divergent findings in some studies may stem from variations in study populations, follow-up durations, and methodologies. For example, the study by Liu indicated that the value of AIP in risk assessment varies significantly with demographic factors, including age and BMI [21]. The distinctive features of our study, including its focus on short-term outcomes in AMI patients and comprehensive adjustments for confounders, contribute to the robustness of our findings. The stronger associations observed in younger patients and those with higher BMI levels suggest potential age- and metabolism-dependent mechanisms influencing the clinical value of the AIP [23, 24].

The biological basis for the nonlinear relationship between the AIP and mortality likely involves complex interactions between lipid metabolism disorders and inflammatory responses. Higher AIP values reflect more severe lipid metabolism disorders and systemic inflammation, which may explain the observed threshold effect [4, 25]. Previous research has shown that elevated AIP levels correlate with increased inflammatory markers and oxidative stress in cardiovascular patients [20, 22]. For instance, elevated levels of inflammatory markers like C-reactive protein and interleukin-6 in high-AIP patients suggest a link between lipid dysregulation and inflammation [5, 26]. Furthermore, the role of oxidative stress in exacerbating these conditions has been well documented, which highlights the importance of monitoring the AIP as a potential reflection of adverse cardiovascular outcomes [11, 27, 28]. At lower AIP values, mortality risks may increase from multiple factors. First, a low AIP often indicates malnutrition, which can lead to compromised immune function and impaired wound-healing capabilities [11, 29]. Such nutritional deficiencies can exacerbate an individual's vulnerability to infections and decrease their ability to recover from illnesses, thus resulting in increased mortality risks among affected individuals. Second, insufficient cholesterol levels, which are reflected in low AIP values, may negatively impact cellular membrane stability and steroid hormone synthesis. This impairment can significantly affect cardiovascular responses to critical illness, as the body relies on adequate cholesterol levels for both hormonal signalling and cellular integrity [29, 30]. Furthermore, a low AIP may serve as a marker for systemic inflammation and oxidative stress. Inflammatory processes are known to disrupt lipid metabolism, ultimately leading to lower HDL-C levels [13]. These mechanisms, combined with the previously discussed adverse effects of high AIP values, contribute to the observed J-shaped relationship between the AIP and mortality.

Results from this research bear substantial clinical significance in the management of AMI patients. The identified AIP threshold of 0.6 represents a simple, cost-effective risk factor that can be readily implemented in routine clinical practice. This threshold provides clinicians with a practical tool for risk stratification, particularly valuable in resource-limited settings where more sophisticated biomarkers may be unavailable [4].

While findings suggest that patients with AIP values exceeding 0.6 may benefit from closer monitoring, prospective trials are needed to evaluate the clinical utility of AIP-guided interventions in AMI patients [31, 32]. The nonlinear relationship that was observed suggests that risk assessment strategies should be tailored according to AIP levels, with particular attention being provided to patients with scores above the 0.6 threshold. This finding could inform the development of personalised treatment approaches that potentially include more aggressive lipid-lowering therapies and lifestyle modifications for high-risk individuals [33]. Although the AIP demonstrates potential value in risk assessment, its routine clinical use for risk stratification in AMI patients should be approached with caution. Current research on the role of the AIP in AMI is largely retrospective, and there is a need for prospective trials to evaluate the effectiveness of targeted interventions based on the reduction in the AIP. Future research needs to concentrate on verifying these results across various populations, investigating the potential benefits of AIP-guided therapeutic interventions, and exploring the integration of the AIP with other established cardiovascular risk markers to increase the precision of risk assessment.

Study strengths and limitations

The study possesses significant methodological advantages that enhance the dependability and applicability of the results. First, the utilisation of the eICU Collaborative Research Database (with data collected from 2,517 patients from multiple centres) ensures robust statistical power and broad representativeness. The study possesses significant methodological advantages that enhance the reliability and applicability of the results: (1) the exclusive recruitment of AMI patients, enabling targeted analysis of this high-risk population; (2) the adoption of a clinically relevant 28-day mortality endpoint; and (3) detailed adjustments for demographic and clinical variables. Second, our comprehensive statistical approach incorporated multiple analytical strategies; specifically, we employed hierarchical adjustment models to control for confounding factors, utilised generalised additive

models to explore nonlinear relationships, and precisely identified threshold effects via recursive algorithm analysis. Third, our rigorous sensitivity analyses (including the conversion of the AIP into categorical variables and the calculation of trend *P* values) strengthened the reliability of our results. The management of missing data via multiple imputation techniques further enhanced the validity of our findings. Additionally, our detailed subgroup analyses revealed important population heterogeneity in the AIP-mortality association, thereby providing valuable insights for clinical risk stratification. Moreover, the calculation of E values for unmeasured confounding factors demonstrated the robustness of our primary findings, thus indicating that only substantial unmeasured confounding factors could nullify the observed associations.

Nevertheless, it is important to recognize several limitations inherent in the study. Firstly, there was an absence of precise timing of lipid measurements relative to the initiation of lipid-lowering therapy. Only 338 (13.43%) patients were receiving lipid-lowering therapy at admission, and the exact timing of the lipid measurements relative to therapy initiation is unknown. This limitation suggests that our results are primarily generalizable to a lipid-lowering-therapy-naïve population rather than the overall AMI patient population. If the AIP values were measured after the initiation of lipid-lowering therapy, the treatment could have affected the AIP levels. Statins and fibrates, which are frequently utilized as lipid-lowering agents, have demonstrated the ability to modify levels of triglycerides and HDL-C [34, 35], thereby impacting AIP calculations. Despite the stratified analysis indicating that the relationship between AIP and mortality was consistent in both groups with ($n=$ 338) and without lipid-lowering treatments ($n=$ 2,179) (Fig. 3), this does not preclude the confounding effect. Future research should focus on obtaining this timing data to clarify the role of lipid-lowering therapy more accurately. Second, although BMI was employed as a stratification factor in our analyses (> 28 vs. ≤ 28 kg/m^2), this variable possesses limitations in assessing metabolic risks, especially among cardiovascular patients. Emerging evidence suggests that alternative indices, such as relative fat mass (RFM), may offer superior predictive value for metabolic syndrome and cardiovascular risks [36]. Future studies should consider incorporating these more precise metabolic markers when data availability permits. Third, the limited sample sizes in several subgroups constrained our capacity to conduct robust subgroup analyses. Specifically, the small numbers of patients with CKD ($n=$ 23), those receiving IABP support ($n=$ 40), and those receiving PCI ($n=$ 102) precluded detailed analyses within these high-risk populations. Larger cohort studies are needed to explore the impacts of the AIP on mortality in AMI patients with CKD, as well as the effects of IABP use and PCI, thereby providing more definitive insights. Fourth, the relatively low rate of RRT (renal replacement therapy) observed in the cohort may reflect both the heterogeneity of the multi-centre ICU database and the specific study design. The variety of ICU types (including medical ICUs, surgical ICUs, cardiac care units, cardiothoracic ICUs, and so on; Table 1) and their distinct admission criteria, combined with the exclusion of repeated ICU admissions and short-stay admissions (< 24 h), may have contributed to the underrepresentation of patients requiring RRT in this study population. While the findings regarding 28-day mortality remain robust, these factors should be considered when interpreting the RRT utilization rates in the study. Additionally, AUC (Area Under the Receiver Operating Characteristic Curve) and calibration plots are widely recognized in predictive model development. However, this research aimed to explore the non-linear relationship between AIP and mortality and identify clinically relevant thresholds. Accordingly, the analysis did not include AUC or calibration plots. Instead, priority was given to maintaining a clear focus on risk stratification and avoiding potential over-interpretation of AIP as a predictive tool in the absence of a fully developed and validated prediction model. Future studies aiming to develop comprehensive predictive models for mortality in AMI patients may consider incorporating these metrics to further evaluate the predictive utility of AIP. Furthermore, the focus of the eICU database on U.S. populations limits the applicability of our results to other ethnic groups or geographical regions. Fifth, the retrospective observational nature of this study allows for the identification of associations between the AIP and mortality, but not for the determination of causality. Even after controlling for several recognized confounding variables, the impact of unmeasured confounders remains a possibility, as indicated by the modest E values. Besides, the brief follow-up duration of 28 days might not capture the complete long-term clinical implications of AIP assessment in AMI patients.

Conclusion

Data from the eICU-CRD might reveal a J-shaped association between the AIP and 28-day mortality in AMI patients. This association highlights AIP's importance in assessing patient risk. Patients exhibiting higher AIP levels, surpassing a certain limit, are at a greater risk of mortality, which may necessitate more rigorous lipid management or closer surveillance. Further studies are needed to validate these results across various populations and to explore the impact of interventions aimed at reducing AIP on patient survival rates.

Abbreviations

AIP	Atherogenic index of plasma
AMI	Acute myocardial infarction
AUC	Area under the receiver operating characteristic curve
BMI	Body mass index
CHF	Congestive heart failure
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
DM	Diabetes mellitus
ESRD	End-stage renal disease
GAM	Generalized additive model
HDL-c	High-density lipoprotein cholesterol
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
ICD-9	International classification of diseases, ninth revision
IQR	Interquartile range
LDL-c	Low-density lipoprotein cholesterol
LRT	Logarithm likelihood ratio test
OR	Odds ratio
PCI	Percutaneous coronary intervention
RRT	Renal replacement therapy
SD	Standard deviation
STEMI	ST-segment elevation myocardial infarction
non-STEMI	Non-ST-segment elevation myocardial infarction
TG	Triglycerides

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02630-6.

Supplementary Material 1.

Acknowledgements
None.

Authors' contributions
YW, extracted the data from the eICU-CRD, designed the study, conducted the statistical analysis, and drafted the manuscript. HF-Z conceived the study, contributed to data interpretation and manuscript revision. All authors read and approved the final manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
The datasets analysed during the current study are available in the eICU-CRD, available at https://physionet.org/content/eicu-crd/2.0/. The code used to analyze eICU-CRD data is publicly available and can be accessed here: https://eicu-crd.mit.edu/eicutables/admissiondrug/.

Declarations

Ethics approval and consent to participate
The eICU-CRD is a publicly available anonymized database and ethical. committee approval was not required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 January 2025 Accepted: 30 May 2025
Published online: 06 June 2025

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